Microbes and Infectious Diseases 2021; 2 (2): 197-203

Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Mini-review article

Diabetes and COVID-19 comorbidity: Matters arising and public health implications

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ARTICLE INFO

Article history:
Received 10 January 2021
Received in revised form 16 February 2021
Accepted 18 February 2021

Keywords:
COVID-19
SARS-CoV-2
Pandemic
Diabetes
Global Health

Abbreviation
COVID-19: Coronavirus disease 2019
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
T1DM: Type 1 diabetes mellitus T2DM: Type 2 diabetes mellitus ARDS: Acute respiratory distress syndrome
COPD: Chronic obstructive respiratory disease
CVD: cardiovascular disease
CKD: Chronic kidney disease
ACE2: Angiotensin-converting enzyme 2
TCZ: Tocilizumab
IL-6: Interleukin-6
WHO: World Health Organization

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has caused significant public health emergency globally. Although the clinical manifestation of COVID-19 is heterogeneous with flu-like symptoms to acute pneumonia and multiple organ failure, its risk, severity and mortality have been associated with diabetes and other non-communicable chronic diseases. Accumulated evidence from emerging epidemiological data has shown enormous global public health concern with hypothetical association existing between COVID-19 and diabetes. Possible mechanisms recently explored as underlying association between COVID-19 and diabetes are hyperglycemia, chronic inflammation, impairment of immune response, increased and prolonged coagulation activity and rapid pancreatic damage by SARS-CoV-2. Furthermore, the discontinuation of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors (ACEI) in individuals with diabetes due to COVID-19 has not been scientifically concluded. The burden associated with COVID-19 and diabetes comorbidity may exacerbate this pandemic, especially in developing countries. However, early diagnosis, comprehension and management of these comorbidities may contribute to better outcomes, hence mitigating severe clinical complications and mortalities.

Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged from Wuhan, China and has spread across the globe causing significantly devastating public health and socioeconomic havocs. Though a respiratory virus, SARS-CoV-2 infection presents a wide range of

DOI: 10.21608/MID.2021.62493.1121
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clinical manifestations which are varied from asymptomatic or mild flu-like symptoms to interstitial and/or severe pneumonia which often progress to acute respiratory distress syndrome (ARDS), multiple organ failure and death [1]. COVID-19 had since reached pandemic proportions and is currently regarded as a great public health threat with no known pharmaceutical interventions or vaccines.

Individuals with COVID-19 alongside other predated disease(s) such as diabetes mellitus are at high risk of severe clinical outcomes with high mortality. Recent studies from hospitalized older and symptomatic COVID-19 patients with comorbidities including diabetes, hypertension, obesity, chronic obstructive respiratory disease (COPD), cardiovascular disease (CVD), chronic kidney disease (CKD), immunodeficiency states and cancer were reportedly associated with more severe clinical outcomes and a higher fatality rate [1,2]. However, patients with type 1 diabetes mellitus (T1DM) are reportedly at higher risk for COVID-19 related death than patients with type 2 diabetes mellitus (T2DM) [3]. So far, clinical and epidemiological data showed multifaceted relationship existing between COVID-19 and diabetes. This article describes the complex, emerging clinical relationship between COVID-19-diabetes comorbidities and the consequential public health implications.

Diabetes comorbidity with acute viral outbreaks

From the available literature, individuals with diabetes are prone to different viral infections, especially pneumonia, flu and influenza [3-5]. When infected with respiratory viruses, individuals with diabetes often develop severe clinical outcomes [6]. During acute infection, high risk that might lead to morbidity and mortality due to suppressed innate and humoral immune function is reported in patients with chronic diseases such as diabetes. Diabetes was regarded as an independent risk factor that led to clinical complications and death in worst cases during the SARS-CoV outbreak between 2002 to 2003 [4,7]. Similarly, the rate of hospitalizations tripled while admission in the intensive care unit (ICU) quadrupled among diabetic individuals during 2009 influenza A (H1N1) infection outbreak [3,5,8]. During the 2012 Middle-East respiratory syndrome coronavirus (MERS-CoV) epidemic, fatal or critical cases were 7.2 to 15.7 times higher among patients with diabetes with a 35.0% higher mortality in MERS-CoV diabetic cohort [5].

In a previous study among Chinese SARS-CoV patients, 51.3% of the study population with no prior history of diabetes nor steroid treatment developed diabetes while on hospitalization [7]. The angiotensin-converting enzyme 2 (ACE2) known to be a major coronavirus receptor also actively participates in the regulation of different physiological processes including glucose metabolism and is also modulated by hyperglycemia and therapeutic measures often used by individuals with diabetes [9]. Angiotensin-converting enzyme 2 has been reported to have a protective role in mitigating the progression and/or severity of cardiovascular and renal complications and has been tipped as a potential treatment target in diabetes management [10,11]. Different studies have revealed the role of ACE2 in the improvement of insulin sensitivity and glucose-mediated insulin release, glycemia levels regulation through direct effects in the pancreas, and decreasing risk of developing type 2 diabetes [12,13].

Taking advantage of ACE2 as receptors for accessing host cells by SARS-CoV-2, ACE2 expression becomes downregulated rapidly upon SARS-CoV-2 infection [14,15] hence, preventing or suppressing the protective roles of ACE2 [16]. However, the mechanisms and effects exerted by coronaviruses against ACE2 protective roles are not yet fully elucidated. Furthermore, COVID-19 patients are liable to suffer pancreatic damage, leading to the worst scenarios in diabetic cohort [17]. To this point, emerging data indicate that diabetic patients are at high risk for developing severe outcomes of COVID-19 infection with higher mortality [18-20]. Possibly, higher stress condition is triggered with the release of high level of hyperglycemic hormones including catecholamine and glucocorticoid hormones in diabetic patients infected with COVID-19 resulting in abnormal glucose variability and higher blood sugar level [17].

Diabetes and COVID-19 Comorbidity: Current clinical evidence and implications

Recently, studies examining the impact of diabetes on COVID-19 severity have emerged. The severity of COVID-19 severity among individuals with diabetes was compared with regards to hospitalization, ICU admission, critical illness, ARDS and occurrence of a composite outcome of diabetes-COVID-19 comorbidity [21]. Although initial reports from different Chinese regions showed variable diabetes prevalence rates among

hospitalized COVID-19 patients, larger studies across China, however, provided consistent prevalence rates of diabetes among COVID-19 patients [17,22,23]. Also, clinical data emerging from around the world especially from hospitalized COVID-19 patients currently shows that diabetes exacerbates SARS-CoV-2 infection severity and increased mortality [18-20,24,25].

In a study involving 7337 COVID-19 patients (median age 54 years) admitted within Hubei province, China, 13.0% (952) were reported to have type 2 diabetes [23]. In other meta-analysis studies involving COVID-19 patients across China, approximately 8–10% had diabetes [26-29]. In two different studies from France and the USA, 11.2 and 23.8% of COVID-19 patients reportedly had diabetes [2,30]. Furthermore, while 27.2% of 1339 COVID-19 patients (mean age 69.1 years) admitted in 7 Madrid hospitals, Spain were reported to have diabetes [18], 14.9% of 410 COVID-19 hospitalized patients (median age 65 years) reportedly had diabetes in an Italian single-center study in Milan, Italy [31]. Among individuals that presented with COVID-19 in the US CDC, 6.4% non-hospitalized patients have diabetes whereas 32.4% and 24.2% admitted to ICUs and non-ICU reportedly have diabetes respectively [32]. Similarly, out of 1000 COVID-19 cases admitted in a hospital in New York, USA, 42.8, 37.8 and 26.0% in ICU, non-ICU and emergency room (ER) respectively have diabetes [24]. Hill et al. [33] also reported that 22.0% of COVID-19 related mortalities from a group of 52 patients admitted in ICU were reported to be diabetic.

For several decades, diabetes has been recognized as a major predisposing factor for higher incidence of infectious diseases and mortality including those caused by respiratory viruses [6]. As such, the onset, progression and severity of SARS-CoV-2 infection may be favored by preexisting diabetes with poor response to the virus by the impaired adaptive immunity and enhanced inflammatory reactions [21]. Chronic pro-inflammatory and pro-coagulant states usually characterized individuals with diabetes, and in some cases, other complications and associated comorbidities [34]. Diabetic individuals are affected by chronic inflammation (little grade) which potentiates severe and/or fatal cases of COVID-19. Various inflammatory factors including interleukin-6 (IL-6) were significantly upregulated in diabetic individuals with COVID-19 when compared with non-diabetic COVID-19 patients [35]. IL-6 as a pleiotropic cytokine often takes part in acute phase inflammatory-like metabolic disorders and cardiovascular diseases. However, the administration of tocilizumab (TCZ) (a monoclonal antibody) tackles the destructive effect of overexpressed IL-6 signaling by blocking the IL-6 receptor. Currently, TCZ has been accepted for the care of some chronic metabolic and autoimmune disorders including severe rheumatoid arthritis, giant cell arthritis and graves orbitopathy [35].

Earlier studies recommended that the use of TCZ could considerably help in the management of COVID-19 pneumonia. Although in some Italian hospitals, TCZ has been used as an off-label drug in the treatment of COVID-19 patients, the drug is currently being examined in an Ad-hoc randomized controlled trial [36]. The drug may be chiefly supportive in diabetic individuals with COVID-19 if the observation could be definite. Together with other drugs known to downregulate IL-6 overexpression due to diabetes-COVID-19 comorbidity, Siltuximab (being a chimeric monoclonal antibody that binds to IL-6) or Janus kinase inhibitors like baricitinib, upadacitinib, and tofacitinib could be used as novel, safe and sustainable therapeutic approach to fight diabetes-COVID-19 comorbidity [35].

In a study conducted in Wuhan, China, at least one episode of hypoglycemia was reported to occur in about 10.0% of COVID-19 cases. The hypoglycemia enhanced platelet reactivity and assemble pro-inflammatory monocytes leads to a massive cardiovascular death among the COVID-19 cases with diabetes [37]. Numerous factors, particularly the impaired immune reaction, heightened inflammatory reaction and hypercoagulable state add to the enhanced diabetes-COVID-19 comorbidity severity and fatality. *In vitro* exposure of pulmonary epithelial cells to high glucose concentration significantly raised influenza virus infection and replication, thus depicting that hyperglycemia may consequentially lead to increased vulnerability to viral infection and replication *in vivo*. High glucose level may also inhibit or slowdown antiviral immune responses by host cells [37].

Although the significance of corticosteroid use on COVID-19 patients is still being examined, recent findings show that it restrains lungs' inflammation. So far, available facts are yet to fully elucidate corticosteroid benefits however, it was

reported to interrupt viral RNA clearance or raise death rate of some complications such as diabetes, vascular necrosis and psychosis [17,38]. To date, the WHO only recommends the use of corticosteroid in clinical trials involving individuals with COVID-19 and not in the general clinical management of COVID-19 cases [17]. There is limited information regarding the management of diabetic patients with COVID-19 as well as individuals who later developed glycemic decomposition after been infected with SARS-CoV-2. Extra caution must be observed in clinical trials assessing the safety and efficacy of corticosteroid in diabetes-COVID-19 comorbidity cases

When not properly managed, individuals with diabetes become vulnerable to infectious diseases, severe clinical complications and most times death [29,39]. The wide use of the anti-malaria drug, hydroxychloroquine (HCQ) both for the treatment and as prophylaxis against COVID-19 in many countries may further exacerbate the diabetes-COVID-19 comorbidity leading to severe clinical outcomes and higher fatality. The hypoglycemic effects of prolonged HCQ use had been established over three decades ago [39]. Therefore, the use of HCQ in managing COVID-19 cases especially among individuals with diabetes may precipitate severe hypoglycemia leading to detrimental outcomes. Consequently, the anti-glycemic effect of HCQ is worth investigating in clinical trials involving individuals with diabetes-COVID-19 comorbidity. This may improve our understanding of the management of COVID-19 patients with diabetes and perhaps unravel prospects for the general improvement in diabetes management once [39].

Furthermore, several experimental results showed that glycemic maintenance may have a positive impact on clinical outcomes among diabetic patients with viral respiratory disease including COVID-19. Therefore, health personnel need to be knowledgeable about the importance of glycemic maintenance among COVID-19 cases. A recent study conducted among COVID-19 patients in China revealed metabolic disorders including significantly higher blood sugar levels than the control during hospitalization [35]. However, the relationship between diabetes and COVID-19 might be bidirectional, with COVID-19 likely worsening pre-existing hyperglycemia or even predisposing diabetes in non-diabetic patients. Since ACE2 is the route of SARS-CoV-2 infection in human cells, the presence of ACE2 in the pancreas and liver may undoubtedly have a potential role of developing impaired insulin secretion or insulin resistance among individuals with COVID-19. Hence, both pancreatic beta-cells and hepatocytes might be infected with SARS-CoV-2 thus, leading to hyperglycemia at least during the acute infection. Although not fully deciphered, the infection of pancreatic beta cells could activate beta-cell autoimmunity in predisposed subjects (in the long term).

Conclusion

COVID-19 pandemic has resulted in a global unprecedented public health and socioeconomic crisis. Although there are yet to be approved therapeutic measures or vaccines against COVID-19, early diagnosis, isolation and management might collectively contribute to a better clinical outcome and COVID-19 control. The impact of COVID-19 on diabetes is a significant risk factor and predicator of severe clinical outcomes and increased fatality. Further studies on the pathophysiological relationship between diabetes and COVID-19 is needed to further elucidate the mechanisms involved and then provide both potent therapeutic and/or preventive measures aimed at mitigating the clinical outcomes of diabetes-COVID-19 comorbidities and fatalities. Standard clinical management of individuals with diabetes-COVID-19 co-infection must be strictly followed by both hospitalized and non-hospitalized patients. Health personnel should give priority attention to glycemic monitoring and control among COVID-19 patients with diabetes.

Acknowledgements

Authors would like to thank the editors for finding this manuscript relevant for publication.

Author Contributions

HA gathered relevant literature, drafted the manuscript. JHA conceptualized the study and edited the first manuscript draft. FM conceptualized of the study, edited and revised manuscript drafts and approved the final version. LYA gathered relevant literature, proof read the manuscript and gave approval for final draft. AY reviewed and revised drafts and approved the final version. RCR edited and reviewed the initial and final manuscript drafts.

Funding

No funding was obtained for writing this manuscript.

Availability of data and materials

All data used in this manuscript are drawn from the references provided.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing Interest

Authors have no conflict of interest

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